A comment on: FLOW®800 allows visualization of hemodynamic changes after extra- to intracranial bypass surgery but not assessment of quantitative perfusion or flow

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FLOW 800 Allows Visualization of Hemodynamic Changes After Extracranial-to-Intracranial Bypass Surgery but Not Assessment of Quantitative Perfusion or Flow

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BACKGROUND: FLOW 800 delivers a color-coded map for snapshot visualization of the temporal distribution dynamics after indocyanine green angiography with post hoc calculation of FLOW 800-specific hemodynamic parameters. However, the value of these parameters regarding quantitative flow assessment remains unclear.

OBJECTIVE: To determine the value of FLOW 800-specific hemodynamic parameters in neurosurgical patients that permit assessment of hemodynamic changes within the microcirculation and macrocirculation.

METHODS: FLOW 800 was performed in 25 patients undergoing superficial temporal artery to middle cerebral artery bypass grafting and in 5 patients undergoing high- or intermediate-flow bypass grafting. The time to half-maximum fluorescence ($t_{1/2max}$) and the cerebral blood flow index were calculated in the recipient vessel (macrocirculation) and the cortical territory (microcirculation) surrounding the anastomosis. For further evaluation, FLOW 800-specific hemodynamic parameters were compared with cortical laser speckle imaging and quantitative Doppler flow within the graft.

RESULTS: FLOW 800 provided color-coded information on the temporospatial distribution dynamics of the dye with excellent assessment of bypass patency. In the recipient vessel and in the cortical territory surrounding the anastomosis, FLOW 800 detected hemodynamic changes after superficial temporal artery to middle cerebral artery bypass grafting in terms of a significant decrease in $t_{1/2max}$ and increase in cerebral blood flow index. Interestingly, comparison of $t_{1/2max}$ with semiquantitative laser speckle imaging-specific cortical perfusion within the microcirculation demonstrated poor agreement, and neither $t_{1/2max}$ nor the cerebral blood flow index within the graft correlated with quantitative graft flow assessed by Doppler.

CONCLUSION: FLOW 800 may detect procedure-related hemodynamic changes within the microcirculation and macrocirculation but should not be used as a stand-alone tool for quantitative flow assessment.

KEY WORDS: Cerebrovascular disease, Extracranial to intracranial bypass, FLOW 800, ICG angiography, Intraoperative CBF assessment, Laser speckle imaging

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ABBREVIATIONS: AI, arbitrary intensity; **CBF,** cerebral blood flow; **CBFi,** cerebral blood flow index; **ICG,** indocyanine green; **ICG-A,** indocyanine green angiography; **H/IFBP,** high-/intermediate-flow bypass; **LSI,** laser speckle imaging; **ROI,** region of interest; **STA-MCA,** superficial temporal artery to middle cerebral artery

Intraoperative indocyanine green (ICG) angiography (ICG-A) was implemented by Raabe and colleagues[1] after the initial description of fluorescent in vivo angiography by Feindel and coworkers[2] and Little et al[3] > 30 years ago. The undisputed value of ICG-A has been shown in numerous publications, leading to routine application of the methodology in various fields of neurovascular surgery requiring fast and simple assessment of vessel patency.[4-7] Although the

method was also shown to be useful for intraoperative cortical perfusion analysis,[8,9] it required offline calculation of hemodynamic parameters.

Recently, FLOW 800 (Carl Zeiss, Oberkochen, Germany) was introduced as a microscope-integrated software tool for instant color-coded visualization and analysis of the temporal distribution dynamics of the fluorescent ICG dye.[10] Against this background, 1 study has also addressed the suitability of FLOW 800 for characterization of perfusion changes within the microcirculation in the acute phase of aneurysmal subarachnoid hemorrhage.[11] However, the value of FLOW 800 for the determination of hemodynamic changes before and after a procedure and the agreement of FLOW 800-specific hemodynamic parameters with more established methods for perfusion and flow assessment remain unclear.

Here, we evaluated FLOW 800-specific hemodynamic parameters in patients undergoing direct surgical revascularization to determine the applicability of FLOW 800 for the assessment of hemodynamic changes within the macrocirculation and microcirculation. To further evaluate FLOW 800-specific hemodynamic parameters, laser speckle imaging (LSI) and quantitative Doppler served as comparative measures for microcirculatory perfusion and macrocirculatory flow, respectively.

METHODS

Patient Population

The study was approved by the local ethics committee of the Charité University Hospital in Berlin, Germany (EA2/139/12). The study included 25 patients who received ICG-A and FLOW 800 before and after superficial temporal artery to middle cerebral artery (STA-MCA) bypass grafting in our institution between July 2010 and January 2013 for treatment of single-photon emission computed tomography-confirmed hemodynamic compromise (n = 9 male patients, n = 16 female patients; median age, 40 years; age range, 1-69 years). In addition, 5 patients underwent high- (saphenous vein) or intermediate- (radial artery) flow bypass (H/IFBP) grafting for treatment of single-photon emission computed tomography-confirmed hemodynamic compromise or a giant aneurysm (n = 3 male patients, n = 2 female patients; median age, 59 years; age range, 44-72 years).

ICG-A and FLOW 800

Intraoperative ICG-A was performed within the same imaging field before and after bypass grafting with a commercially available operating microscope (Zeiss OPMI Pentero, Carl Zeiss Meditec, Oberkochern, Germany) equipped with a fluorescent light source (wave length, 700-850 nm) and an infrared-sensitive camera. The microscope was positioned perpendicular to the area of investigation at a distance of 300 mm. For each ICG analysis, room lights were dimmed, and a constant body weight-adapted dose of 0.25 mg/kg ICG (Pulsion Medical Systems, Munich, Germany) dissolved in 5 mL distilled water was injected through a central venous catheter as a bolus, followed by a 10-mL bolus of sterile saline. The emission signal of the fluorescent light was recorded, followed by the generation of color-coded transit time maps of the fluorescent dye by the FLOW 800 software for visualization of macrocirculatory flow and microcirculatory perfusion. The color-coded maps were automatically calculated and instantly viewed immediately after each ICG recording. Region of interest (ROI) placement and analysis were performed at a later time point after surgery.

Analysis of FLOW 800-Specific Hemodynamic Parameters

To test the suitability of FLOW 800 for hemodynamic assessment within the cortical macrocirculation and microcirculation, FLOW 800-specific hemodynamic parameters were determined within the recipient vessel and the cortical area surrounding the anastomosis before and after STA-MCA bypass grafting and within the bypass graft of all STA-MCA and H/IFBP patients. For this purpose, standardized ROIs were manually placed within the macrovascular and microvascular compartments. For analysis of the macrovasculature, 1 ROI was placed within the recipient vessel before and after bypass grafting and within the bypass graft after completion of the anastomosis. For analysis of the microvasculature, 5 ROIs were placed within the cortical area surrounding the site of the anastomosis.

For each ROI, we analyzed hemodynamic parameters that were either dependent (cerebral blood flow [CBF] index [CBFi]) or independent (time to half-maximum fluorescence [$t_{1/2max}$]) of the maximum fluorescence intensity (arbitrary intensity [AI]) of the ICG dye (Figure 1). The $t_{1/2max}$ was calculated as the time interval between 0% and 50% of the maximum fluorescence intensity. CBFi was calculated according to the definition by Kuebler and colleagues[12] as follows: maximum fluorescence intensity (AI)/rise time (s) = CBFi (AI/s). Rise time was defined as the time interval between 10% and 90% of the maximum fluorescence intensity. In STA-MCA bypass patients, the percent change of $t_{1/2max}$ and CBFi before and after bypass grafting was additionally determined. Parameters were calculated automatically with the microscope-integrated FLOW 800 software analysis tool.

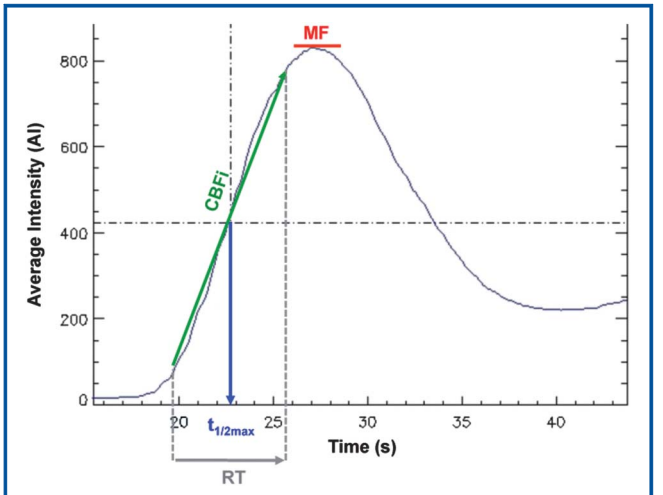

FIGURE 1. *Indocyanine green fluorescence transit-time curve illustrating the different hemodynamic FLOW 800 parameters: AI, fluorescence intensity displayed in arbitrary intensity units; CBFi, cerebral blood flow index defined as the ratio of maximum fluorescence intensity (AI) and rise time (seconds); MF, maximum fluorescence intensity; RT, rise time defined as the time interval between 10% and 90% of the maximum fluorescence intensity; $t_{1/2max}$, time to half-maximum fluorescence.*

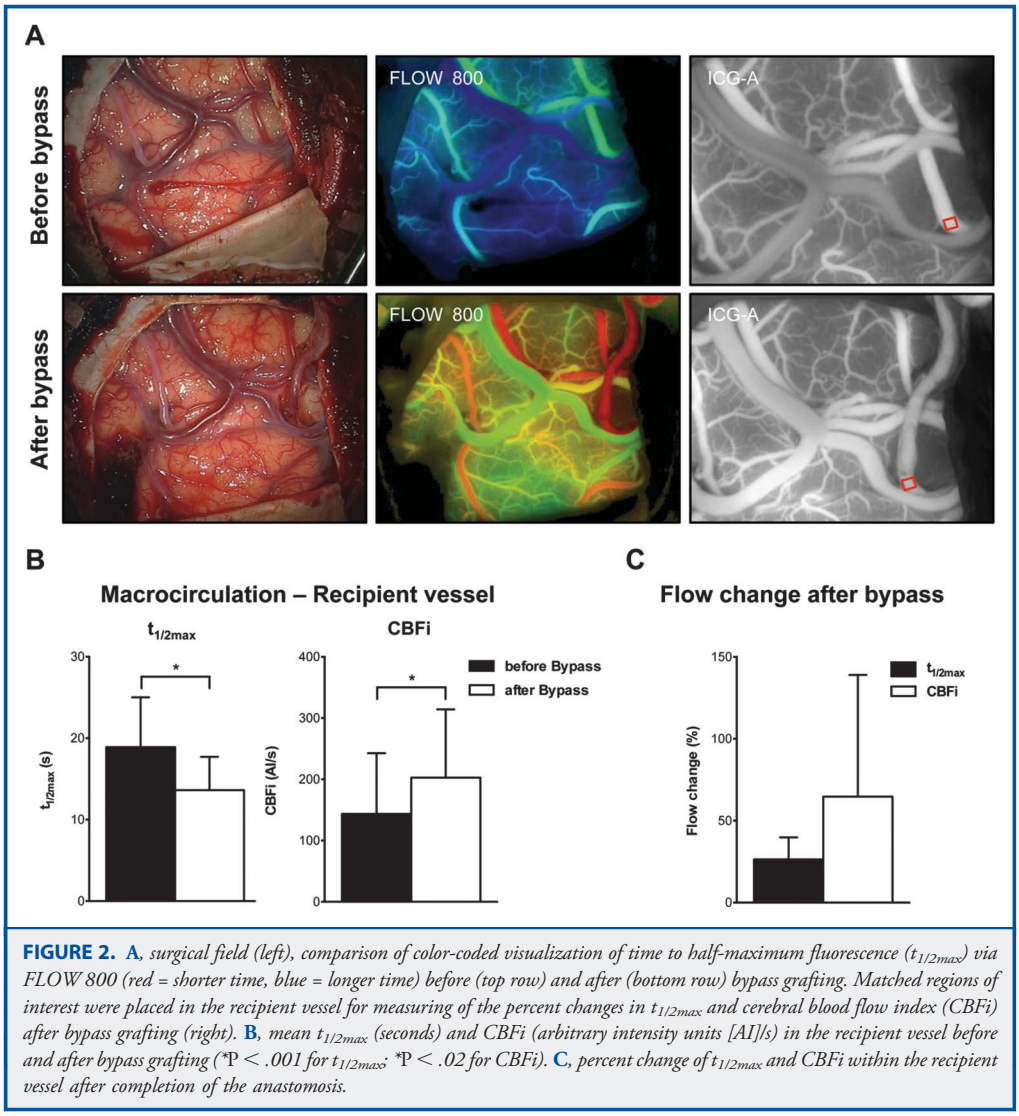

FIGURE 2. **A**, *surgical field (left), comparison of color-coded visualization of time to half-maximum fluorescence ($t_{1/2max}$) via FLOW 800 (red = shorter time, blue = longer time) before (top row) and after (bottom row) bypass grafting. Matched regions of interest were placed in the recipient vessel for measuring of the percent changes in $t_{1/2max}$ and cerebral blood flow index (CBFi) after bypass grafting (right).* **B**, *mean $t_{1/2max}$ (seconds) and CBFi (arbitrary intensity units [AI]/s) in the recipient vessel before and after bypass grafting (*P < .001 for $t_{1/2max}$; *P < .02 for CBFi).* **C**, *percent change of $t_{1/2max}$ and CBFi within the recipient vessel after completion of the anastomosis.*

LSI and FLOW 800

To investigate whether microcirculatory perfusion assessment with FLOW 800 is comparable to semiquantitative CBF measurements by LSI, normalized FLOW 800-specific perfusion ($t_{1/2max}$) and LSI-specific perfusion (CBF flux) were compared within the same cortical territory.

Intraoperative LSI was performed in 7 patients with hemodynamic impairment following ICG-A before and after STA-MCA bypass grafting and is methodologically described elsewhere in detail.[13] A full-field laser speckle device (MoorFLPI, Moor Instruments Ltd, Axminster, United Kingdom) was positioned 300 mm perpendicular to the exposed cortical surface. In each patient, a 5 × 5-cm imaging field with fixed focal and zoom settings was adjusted corresponding to the imaging field visualized during ICG-A. Cortical perfusion was visualized and recorded as a 2-dimensional, color-coded map (red indicates high flow; blue indicates low flow) in an LSI-specific arbitrary perfusion unit (CBF flux). For perfusion assessment before and after bypass grafting, two 120-second measurements of cortical CBF flux were obtained within identical imaging fields of the same cortical areas. To calculate CBF flux within the imaging fields before and after bypass grafting, 16 ROIs of identical size and shape were positioned outside the large surface vasculature with purpose-designed data acquisition software (MoorFLPI measurement software, version V3.0, Moor Instruments) after 16 identical ROIs were positioned within the corresponding areas of the FLOW 800 measurements in the same 7 patients. For comparison before and after STA-MCA bypass grafting, ROIs were positioned in corresponding areas. The mean CBF flux was calculated for each ROI, and the LSI-specific perfusion was determined as the mean CBF flux during a 60-second plateau of the 120-second perfusion measurement. In cases when identical ROI placement was not possible (ie, because of brain shift or obstruction of the imaging field), the ROIs were excluded from analysis.

Despite the fact that ROIs within the FLOW 800 software were selected in a standardized size and shape, there was no direct possibility to obtain information on the ROI dimensions. Therefore, comparability

between FLOW 800 and LSI was ensured by anatomic surface matching of the ROIs. As a hemodynamic FLOW 800 parameter, we selected $t_{1/2max}$ because it is based only on time, not the absolute value of the fluorescence intensity, which results in less variability. In addition, $t_{1/2max}$ is useful for routine application because it is automatically calculated on placement of the ROI.

To compare FLOW 800 with LSI-specific perfusion parameters, $t_{1/2max}$ and CBF flux of each individual ROI were normalized to relative (percent) perfusion compared with 100% of baseline perfusion, which was defined as the mean $t_{1/2max}$ or CBF flux of all ROIs in each individual patient before bypass grafting. The percent perfusion change after bypass grafting was calculated from the change in the FLOW 800- and LSI-specific perfusion parameters.

Quantitative Doppler Measurements and FLOW 800

To clinically evaluate FLOW 800 for blood flow assessment in the macrovasculature, FLOW 800-specific parameters within the bypass graft of all STA-MCA and H/IFBP patients were compared with quantitative flow within the bypass obtained by the Charbel Micro-Flowprobe connected to the Transsonic HT 313 single-channel flow meter (Transsonic Systems Inc, Ithaca, New York).[14]

Statistical Analysis

Values are given as mean ± SD. Statistical analysis was performed with GraphPad Prism (version 6.0, GraphPad Software, San Diego, California). Comparisons between groups were performed with the Student *t* test or Mann-Whitney *U* test as applicable. To analyze whether relative perfusion assessment with FLOW 800 agrees with perfusion assessment by LSI, the Bland-Altman method was applied. For comparison of the mean arterial blood pressure during LSI and the total relative perfusion change after bypass grafting, a Wilcoxon matched-pairs signed-rank test was used. Statistical significance was set at $P < .05$.

RESULTS

Bypass Patency

ICG-A and subsequent FLOW 800 provided instant color-coded information on the temporospatial distribution profile of the fluorescent dye, demonstrating positive bypass patency in all cases.

$t_{1/2max}$ and CBFi Before and After Bypass Grafting

Bypass grafting resulted in a significant decrease in the mean $t_{1/2max}$ from 18.91 ± 6.1 to 13.62 ± 4.1 seconds ($P < .001$) and

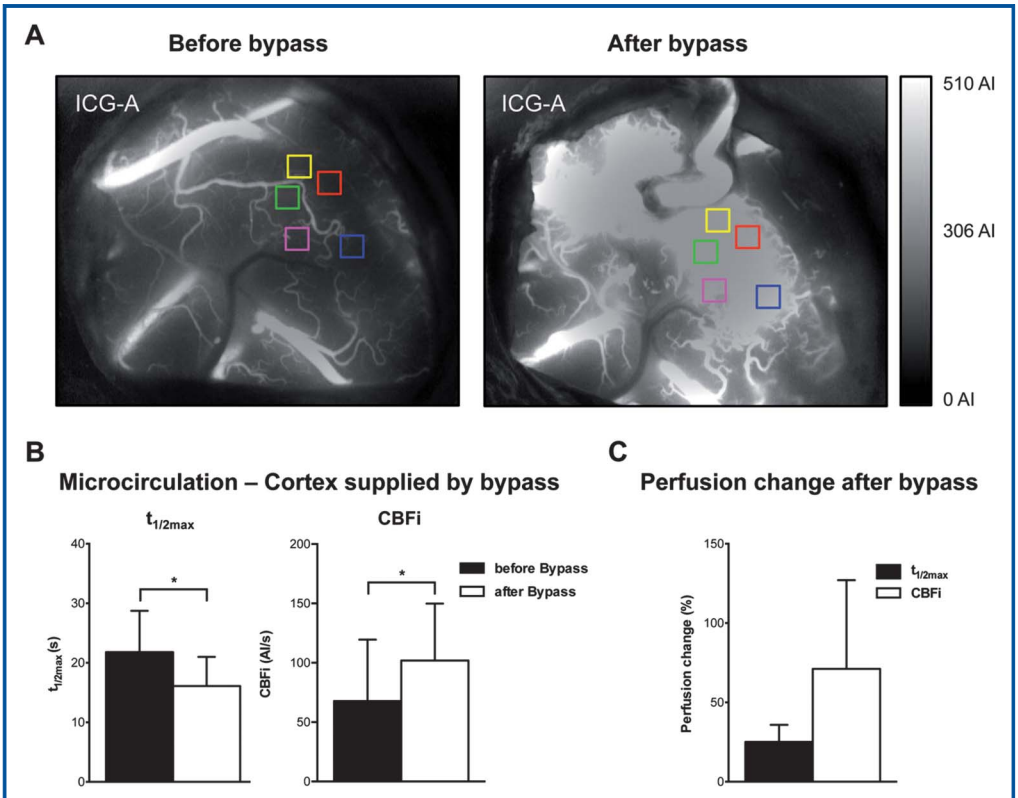

FIGURE 3. **A**, *corresponding indocyanine green fluorescence angiographic (ICG-A) images with 5 matched regions of interest before and after bypass grafting from the points where FLOW 800-specific perfusion parameters were calculated.* **B**, *mean time to half-maximum fluorescence ($t_{1/2max}$; seconds) and cerebral blood flow index (CBFi; arbitrary intensity units [AI]/s) within the cortical territory supplied by the bypass before and after bypass grafting (*P < .002 for $t_{1/2max}$; *P = .005 for CBFi).* **C**, *percent change of $t_{1/2max}$ and CBFi within the cortical territory supplied by the bypass after completion of the anastomosis.*

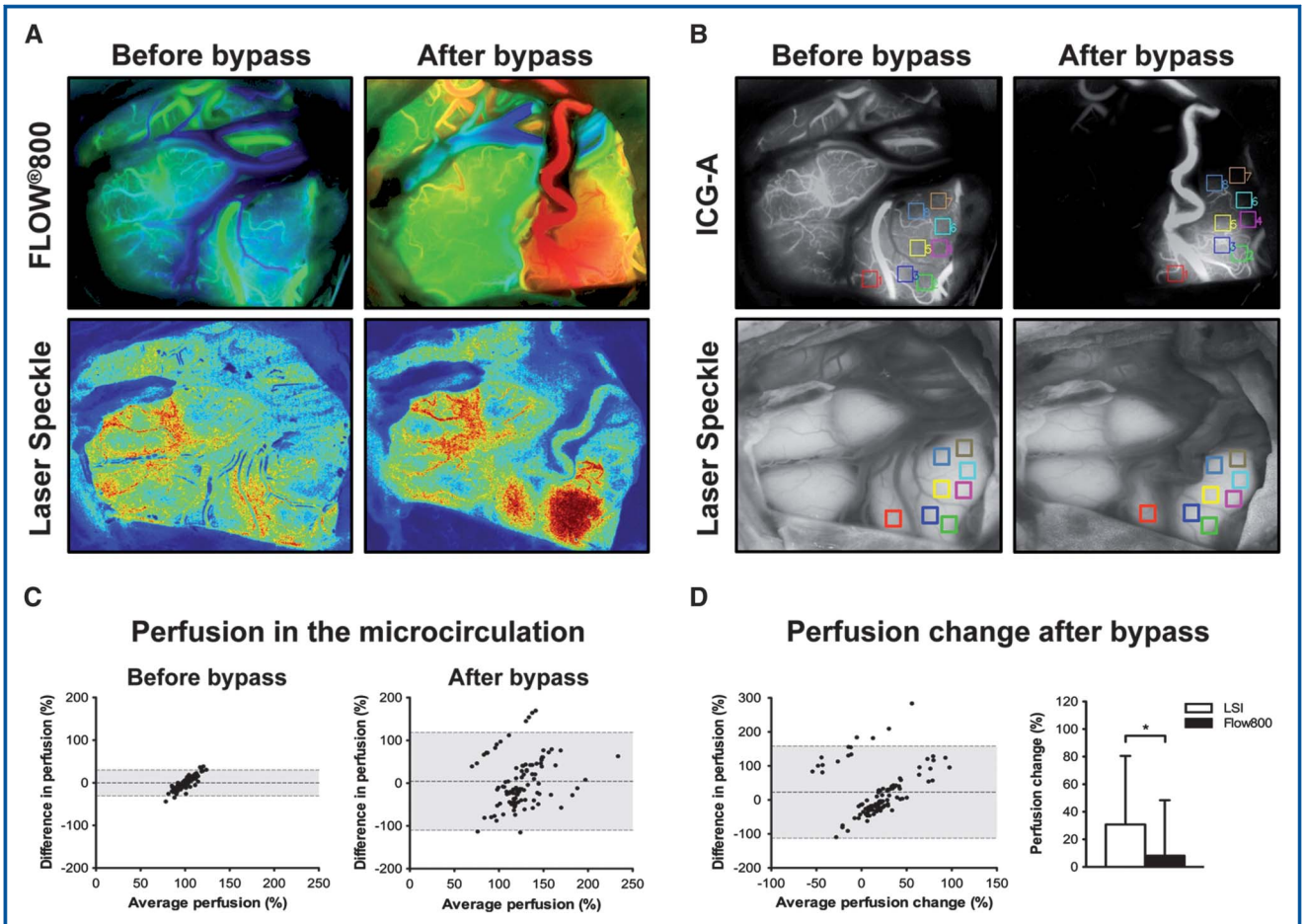

FIGURE 4. **A**, *comparison of the color-coded visualization of the mean time to half-maximum fluorescence ($t_{1/2max}$; FLOW 800, top; red = shorter time, blue = longer time) and cerebral blood flow (CBF) flux (laser speckle imaging [LSI], bottom; red = high flow, blue = low flow) in a patient before and after bypass grafting.* **B**, *corresponding indocyanine green fluorescence angiographic (ICG-A) and LSI images show 8 of 16 matched regions of interest before and after bypass grafting from which $t_{1/2max}$ and CBF flux were calculated.* **C**, *cortical perfusion. Bland-Altman analysis of normalized relative (percent) $t_{1/2max}$ and CBF flux before (left) and after (right) bypass grafting demonstrates poor agreement between FLOW 800 and LSI.* **D**, *cortical perfusion change after bypass. Bland-Altman analysis of the bypass-associated perfusion change shows poor agreement between $t_{1/2max}$ and CBF flux (left). Percent change of $t_{1/2max}$ and CBF flux within the microcirculation compared with baseline (right; *P < .05).*

an increase in the mean CBFi from 143.61 ± 99.2 to 202.8 ± 111.6 AI/s in the recipient vessel ($P < .02$; Figure 2A and 2B). The percent flow change after bypass grafting was determined at 26.4% for $t_{1/2max}$ and 64.71% for CBFi (Figure 2C).

In the downstream cortical territory, bypass grafting led to a significant decrease in the mean $t_{1/2max}$ from 21.81 ± 6.9 to 16.12 ± 4.9 seconds ($P < .002$) and an increase of the mean CBFi from 67.84 ± 51.7 to 101.92 ± 47.9 AI/s ($P = .005$; Figure 3A and 3B). The percent perfusion change after bypass grafting was determined at 25.12% for $t_{1/2max}$ and 71.13% for CBFi (Figure 3C).

Microcirculatory Flow Assessment by FLOW 800 and LSI

Perfusion maps of FLOW 800 and LSI with placement of the ROIs before and after bypass grafting are shown in Figure 4A and 4B. A total of 102 corresponding ROIs were analyzed. Before bypass grafting, we determined a mean perfusion difference of −0.203% (95% confidence interval, −3.21 to 2.83) between FLOW 800 and LSI with 95% limits of agreement ranging from −30.42% to 30.01%. After bypass grafting, the mean difference was determined at 4.3% (95% confidence interval, −7.14 to 15.76) with limits of agreement ranging from −110% to 118.6% (Figure 4C). Overall, LSI detected a perfusion change after bypass grafting of 31 ± 50% compared with a significantly lower perfusion change of 8 ± 40% ($P < .05$) detected by FLOW 800. The mean difference in the percent perfusion change detected by FLOW 800 or LSI after bypass grafting was 22.66% (95% confidence interval, 9.08 to 36.23) with limits of agreement ranging from −112.8% to 158.1% (Figure 4D). Mean arterial blood pressure during LSI did not

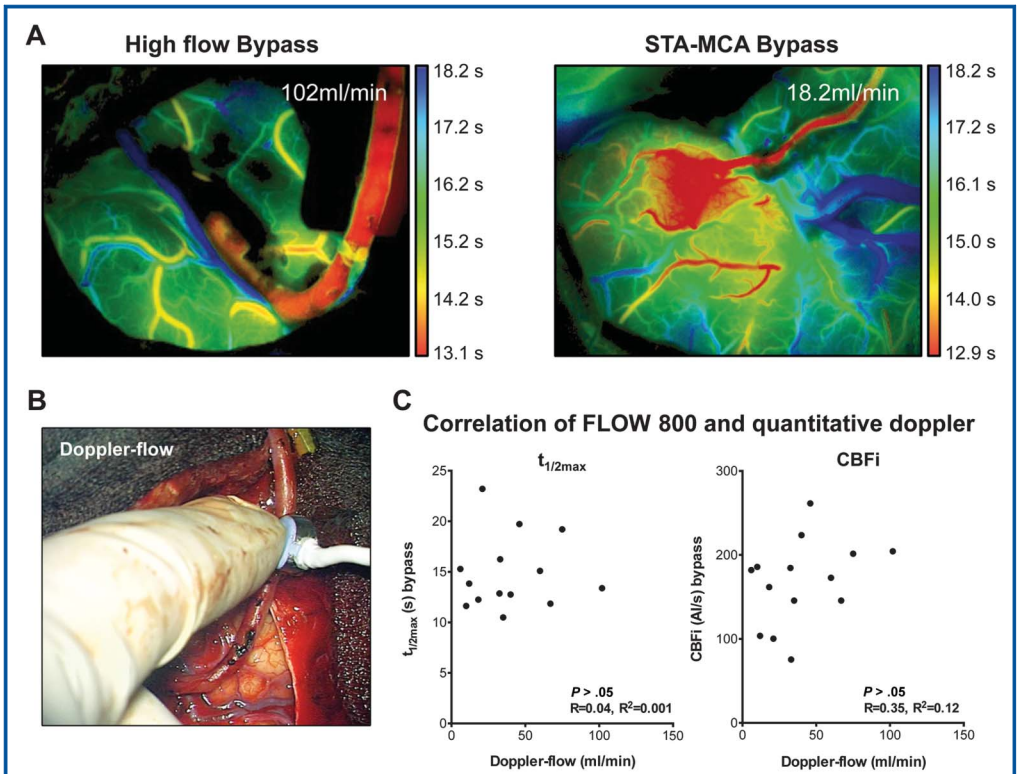

FIGURE 5. **A**, *FLOW 800 images in a patient with high-flow bypass (HFBP; left) and superficial temporal artery to middle cerebral artery (STA-MCA) bypass (right) illustrate the lack of a correlation of quantitative Doppler flow (top right-hand corner) and color-coded transit time of the fluorescent dye. Despite similar transit-time patterns of the fluorescent dye (scale bars on the right), a marked difference in quantitative graft flow exists.* **B**, *acquisition of quantitative graft flow after HFBP surgery.* **C**, *dot plots of CBFi (arbitrary intensity units [AI]/s) vs Doppler (left) and time to half-maximum fluorescence ($t_{1/2max}$) vs Doppler (right) showing no correlation between FLOW 800-specific parameters and absolute blood flow within the bypass graft.*

differ before (96 ± 17 mm Hg) and after (94 ± 21 mm Hg) bypass grafting.

Correlation of FLOW 800 and Quantitative Graft Flow

In 14 STA-MCA and H/IFBP patients, quantitative Doppler measurements were obtained in the bypass graft (Figure 5B). Mean absolute graft flow was 24 ± 14 mL/min in the STA-MCA group (n = 9) and 69 ± 23 mL/min in the H/IFBP group (n = 5). Comparison of quantitative Doppler flow within the bypass graft with $t_{1/2max}$ and CBFi did not show significant correlations (Figure 5C). Furthermore, no correlation was detected between Doppler flow and $t_{1/2max}$ or CBFi in the downstream cortical territory supplied by the graft (data not shown).

DISCUSSION

During extracranial-intracranial bypass surgery, FLOW 800 provided intraoperative, color-coded maps on macrocirculatory and microcirculatory flow in high temporospatial resolution. However, comparison of FLOW 800 with a semiquantitative method for perfusion assessment (LSI) showed poor agreement, and comparison of FLOW 800 parameters within the bypass graft with quantitative Doppler lacked correlation. Therefore, FLOW 800 parameters should not be interpreted as stand-alone measures for quantitative flow.

The calculation of hemodynamic parameters based on the distribution dynamics of fluorescent dye has been proven useful in animal models and in clinical studies,[8,12,15,16] but the applicability and robustness of these parameters for the estimation of tissue perfusion and blood flow are unclear. For the purpose of evaluating FLOW 800-specific hemodynamic parameters in our study, we chose patients undergoing cerebral bypass surgery because it permits an analysis of blood flow within the macrocirculation, ie, the recipient vessel and bypass graft, but also of perfusion changes within the further downstream microcirculation. Second, STA-MCA bypass surgery is a highly standardized procedure, which increases the robustness of the analysis and facilitates the comparison of individual results. Third, measurements of the cortical surface can be performed easily compared with flow assessment during aneurysm surgery, eg, when the imaging field may be obscured because of the more deeply situated imaging field.

FLOW 800 does not provide absolute values of blood flow and perfusion. However, $t_{1/2max}$ and CBFi before and after bypass grafting showed significant changes in the cortical perfusion profile and in the recipient vessel after completion of the anastomosis, which is in line with a recent report.[17] As expected, CBFi was subject to a high variability as a result of the interindividual differences in maximum fluorescence intensity. This effect could be caused by inhomogeneous mixing of the dye or variations of the speed of the bolus injection, which are basic requirements for valid hemodynamic perfusion assessment through indicator dilution approaches. In the present study, all ICG injections were performed following a fixed protocol, including identical concentration, volume, and central venous injection sites at a mean arterial blood pressure target of 90 to 100 mm Hg. Nevertheless, differences in blood volume, cardiac output, and the individual angioarchitecture, particularly the cerebrovascular collateral network, may hamper interindividual comparability.[12,15,17]

Noninvasive imaging modalities for quantitative CBF assessment such as PET are hampered by logistical and financial constraints. Currently, there is no routine method offering intraoperative visualization and quantitative measurement of cortical microcirculatory perfusion in high-temporospatial resolution. In view of recent findings suggesting that FLOW 800 could be used for the assessment of quantitative CBF and early identification of potentially harmful perfusion changes,[10,11,17] we sought to compare FLOW 800 with more established methods for continuous and noninvasive intraoperative real-time assessment of perfusion and flow such as LSI and quantitative Doppler, respectively.[13,14,18] Although $t_{1/2max}$ is dependent on the nature of the injection (ie, the site and speed of the injection), we selected $t_{1/2max}$ for comparison with LSI because $t_{1/2max}$ is based on the transit time of the dye, not the absolute fluorescence intensity, which may render $t_{1/2max}$ less variable than CBFi under standardized ICG administration. In addition, $t_{1/2max}$ is of practical interest because it is used for the generation of the color-coded FLOW 800 perfusion maps. Although both FLOW 800 and LSI showed significant perfusion changes in the cortical microcirculation after patent bypass grafting, normalized FLOW 800-specific and LSI-specific perfusion parameters showed poor agreement. First, this may be explained by the fact that LSI permits continuous real-time calculation of semiquantitative arbitrary perfusion units (CBF flux), whereas $t_{1/2max}$ captures only a snapshot of the hemodynamic situation. Second, FLOW 800 does not consider the diameters of the individual vessels; consequently, calculation of perfusion in terms of blood flow velocity is not possible. Third, the temporal dynamics of $t_{1/2max}$ are highly dependent on the cerebrovascular angioarchitecture; in patients with a patent bypass, for example, the donor vessel is usually the first vessel showing contrast enhancement within the imaging field. However, this early contrast enhancement does not automatically let the surgeon conclude that blood flow in the donor vessel is higher than in a later perfused cortical artery because here contrast enhancement could naturally be expected to occur later owing to the longer distance that the contrast dye needs to travel. This hypothesis was confirmed after comparing FLOW 800 and quantitative graft flow of STA-MCA and H/IFBP patients in whom FLOW 800-specific flow and perfusion in the bypass and the downstream microcirculation did not correlate with quantitative Doppler flow within the graft. An example is provided in Figure 5A, which presents color-coded FLOW 800 maps of $t_{1/2max}$ for a patient receiving an HFBP and another in whom STA-MCA bypass grafting was performed; despite a similar color-coded $t_{1/2max}$ within the imaging field, a marked difference in actual graft flow existed. Therefore, FLOW 800-specific hemodynamic parameters appear useful mainly for comparison before and after a treatment and for regional comparison within the same patient, but not for assessment of quantitative flow.

CONCLUSION

The microscope-integrated FLOW 800 system is smoothly integrated into the surgical workflow and is easy to use. Instant color-coded mapping of hemodynamic parameters permits high-resolution visualization of the vasculature within the imaging field and allows immediate interpretation, which could be helpful for the selection of a suitable recipient vessel during bypass surgery or visualization of intrapatient hemodynamic changes. A main limitation, however, is that FLOW 800 is not capable of continuous real-time assessment of flow, and FLOW 800-specific hemodynamic parameters should not be used for quantitative blood flow assessment.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Raabe A, Beck J, Gerlach R, Zimmermann M, Seifert V. Near-infrared indocyanine green video angiography: a new method for intraoperative assessment of vascular flow. *Neurosurgery*. 2003;52(1):132-139; discussion 139.
2. Feindel W, Yamamoto YL, Hodge CP. Intracarotid fluorescein angiography: a new method for examination of the epicerebral circulation in man. *Can Med Assoc J*. 1967;96(1):1-7.
3. Little JR, Yamamoto YL, Feindel W, Meyer E, Hodge CP. Superficial temporal artery to middle cerebral artery anastomosis: intraoperative evaluation by fluorescein angiography and xenon-133 clearance. *J Neurosurg*. 1979;50(5):560-569.
4. Woitzik J, Horn P, Vajkoczy P, Schmiedek P. Intraoperative control of extracranial-intracranial bypass patency by near-infrared indocyanine green videoangiography. *J Neurosurg*. 2005;102(4):692-698.
5. Hanggi D, Etminan N, Steiger HJ. The impact of microscope-integrated intraoperative near-infrared indocyanine green videoangiography on surgery of arteriovenous malformations and dural arteriovenous fistulae. *Neurosurgery*. 2010; 67(4):1094-1103; discussion 1103-1104.
6. de Oliveira JG, Beck J, Seifert V, Teixeira MJ, Raabe A. Assessment of flow in perforating arteries during intracranial aneurysm surgery using intraoperative near-infrared indocyanine green videoangiography. *Neurosurgery*. 2007;61(3 suppl):63-72; discussion 72-73.
7. Raabe A, Nakaji P, Beck J, et al. Prospective evaluation of surgical microscope-integrated intraoperative near-infrared indocyanine green videoangiography during aneurysm surgery. *J Neurosurg*. 2005;103(6):982-989.

8. Czabanka M, Peña-Tapia P, Schubert GA, Woitzik J, Vajkoczy P, Schmiedek P. Characterization of cortical microvascularization in adult moyamoya disease. *Stroke*. 2008;39(6):1703-1709.
9. Woitzik J, Peña-Tapia PG, Schneider UC, Vajkoczy P, Thomé C. Cortical perfusion measurement by indocyanine-green videoangiography in patients undergoing hemicraniectomy for malignant stroke. *Stroke*. 2006;37(6):1549-1551.
10. Kamp MA, Slotty P, Turowski B, et al. Microscope-integrated quantitative analysis of intraoperative indocyanine green fluorescence angiography for blood flow assessment: first experience in 30 patients. *Neurosurgery*. 2012;70(1 suppl operative):65-73; discussion 73-74.
11. Schubert GA, Seiz-Rosenhagen M, Ortler M, Czabanka M, Scheufler KM, Thome C. Cortical ICG videography for quantification of acute hypoperfusion after subarachnoid hemorrhage: a feasibility study. *Neurosurgery*. 2012;71(2 suppl Operative):260-267; discussion 267-268.
12. Kuebler WM, Sckell A, Habler O, et al. Noninvasive measurement of regional cerebral blood flow by near-infrared spectroscopy and indocyanine green. *J Cereb Blood Flow Metab.* 1998;18(4):445-456.
13. Hecht N, Woitzik J, König S, Horn P, Vajkoczy P. Laser speckle imaging allows real-time intraoperative blood flow assessment during neurosurgical procedures. *J Cereb Blood Flow Metab.* 2013;33(7):1000-1007.
14. Charbel FT, Hoffman WE, Misra M, Ostergren L. Ultrasonic perivascular flow probe: technique and application in neurosurgery. *Neurol Res.* 1998;20(5):439-442.
15. Habazettl H, Athanasopoulos D, Kuebler WM, et al. Near-infrared spectroscopy and indocyanine green derived blood flow index for noninvasive measurement of muscle perfusion during exercise. *J Appl Physiol (1985).* 2010;108(4):962-967.
16. Kuebler WM. How NIR is the future in blood flow monitoring? *J Appl Physiol (1985).* 2008;104(4):905-906.
17. Uchino H, Nakamura T, Houkin K, Murata J-I, Saito H, Kuroda S. Semi-quantitative analysis of indocyanine green videoangiography for cortical perfusion assessment in superficial temporal artery to middle cerebral artery anastomosis. *Acta Neurochir (Wien).* 2013;155(4):599-605.
18. Woitzik J, Hecht N, Pinczolits A, et al. Propagation of cortical spreading depolarization in the human cortex after malignant stroke. *Neurology*. 2013;80 (12):1095-1102.

COMMENTS

The authors analyzed their data retrospectively to determine the value of FLOW®800-specific hemodynamic parameters in neurosurgical patients that permit assessment of hemodynamic changes within the microcirculation and macrocirculation. As they show, instant color-coded mapping of hemodynamic parameters permits high-resolution visualization of the vasculature within the imaging field and allows immediate interpretation, which could be very helpful for the selection of a suitable recipient vessel particularly during bypass surgery.

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Microscope-integrated indocyanine green (ICG) videoangiography (ICG-VA) allows a simple, reliable, fast, and noninvasive intraoperative observation and documentation of blood flow during neurosurgical procedures. ICG-VA imaging quality and spatial and temporal resolution enable a real-time assessment of the cerebral circulation, with distinct evaluation of the arterial, capillary, and venous phases.[1,2] ICG-VA technology is currently very popular in neurosurgery, representing a very useful instrument for a real-time evaluation of the angioanatomy, blood flow direction, and thus intraoperative decision making.[1,6-8]

Recently, a microscope-integrated module has become available to allow "quantification" of ICG transit after intravenous application: the FLOW®800 (Zeiss, Oberkochen, Germany). It enables instant color-coded map visualization and analysis of the temporospatial distribution of the ICG dye. Instant color-coded visualization of the ICG transit time curves permit a high-resolution visualization of the vasculature within the image field and of the blood flow and perfusion. This tool has opened new possibilities in assessing blood flow in cerebral vessels and brain tissue, which might give important information for detecting intraoperative hemodynamic changes.[6] With this technology, it is not necessary to move the microscope away from the operative field. Furthermore, FLOW®800-assisted hemodynamic measurements may be repeated almost as many times as needed (within a maximum daily dose of 5 mg/kg), with a delay of 15 minutes for dye clearance between 2 consecutive ICG administrations. One of the major limitations of this technology is that the observable territory is restricted to the microscopic view. Finally, optimization and standardization of factors such as ICG injection rate and dose, as well as the surrounding environmental conditions (ie, illumination) and systemic hemodynamic factors (eg, maintenance of blood pressure), appear crucial for evaluation of ICG-fluorescence based data.[9,10]

In this well-written article, the authors seek to determine the value of FLOW®800 in the assessment of hemodynamic changes within the microcirculation and macrocirculation after extra-to-intracranial bypass. The experimental work was designed to perform a comparison between FLOW®800-specific hemodynamic parameters and 2 different independent methods, laser speckle imaging (as a comparative measure for the microcirculation) and quantitative Doppler flow (as a comparative measure for the macrocirculation).

Laser speckle imaging was recently demonstrated to be an applicable tool for intraoperative continuous, noninvasive real-time visualization and assessment of microcirculatory perfusion (with semiquantitative blood flow assessment).[5] Its limitations include the fact that this method is not integrated into the surgical microscope and can analyze only the part of the brain tissue that is exposed during surgery. It has a lower spatial resolution compared with ICG-VA, and it does not permit interpretation of flow direction, vessel stenosis, or patency of a bypass anastomosis. Therefore, for perfusion visualization within intracranial vessels, ICG-VA should remain the method of choice.

Quantitative Doppler flow assessment within the bypass was performed in this study by use of the Charbel Micro-Flowprobe connected to the Transsonic HT 313 single-channel flow meter (Transsonic Systems Inc, Ithaca, New York).

Both FLOW®800 and LSI showed significant hemodynamic changes in cortical microcirculation after bypass surgery. However, the comparison between these 2 methods showed poor agreement. In addition, the comparison with quantitative Doppler lacked correlation. No correlation has been shown between color-coded transit time of the ICG and quantitative color Doppler, and no correlation was demonstrated between FLOW®800-specific parameters and absolute blood flow within the bypass graft.

The FLOW®800 system is an easy-to-handle microscope-integrated tool that allows instant color-coded visualization of the ICG transition and permits high-resolution visualization of the angioanatomy. An interesting application, as mentioned by the authors, can be its use in selecting a suitable recipient vessel in bypass surgery. FLOW®800 is also able to show cortical hemodynamic changes after bypass surgery, and the color-coded visualization is very easy to interpret. However, as demonstrated here, FLOW®800 does not allow a continuous real-time assessment of flow and should not be used "quantitative blood flow assessment."

This article represents an important contribution to the literature in that it warns against potential pitfalls of new techniques. Further research

and studies aimed at finding an easy-to-use, efficient, and possibly cost-effective routine method offering intraoperative visualization and quantitative measurement of cortical microcirculatory perfusion in high spatial resolution are needed. We strongly encourage further developments of such technologies.

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1. Dashti R, Laakso A, Niemelä M, Porras M, Hernesniemi J. Microscope-integrated near-infrared indocyanine green videoangiography during surgery of intracranial aneurysms: the Helsinki experience. *Surg Neurol.* 2009;71(5):543-550.
2. Raabe A, Beck J, Gerlach R, Zimmermann M, Seifert V. Near-infrared indocyanine green video angiography: a new method for intraoperative assessment of vascular flow. *Neurosurgery*. 2003;52(1):132-139; discussion 139.
3. Bruneau M, Sauvageau E, Nakaji P, et al. Preliminary personal experiences with the application of near-infrared indocyanine green videoangiography in extracranial vertebral artery surgery. *Neurosurgery*. 2010;66(2):305-311; discussion 311.
4. Esposito G, Durand A, van Doormaal TP, Regli L. Selective-targeted extra-intracranial bypass surgery in complex middle cerebral artery aneurysms: correctly identifying the recipient artery using indocyanine green video-angiography. *Neurosurgery*. 2012;71(2 suppl operative):ons274-ons84; discussion ons284-ons285.
5. Hecht N, Woitzik J, Konig S, Horn P, Vajkoczy P. Laser speckle imaging allows real-time intraoperative blood flow assessment during neurosurgical procedures. *J Cereb Blood Flow Metab.* 2013;33(7):1000-1007.
6. Kamp MA, Slotty P, Turowski B, et al. Microscope-integrated quantitative analysis of intraoperative indocyanine green fluorescence angiography for blood flow assessment: first experience in 30 patients. *Neurosurgery*. 2012;70(1 suppl operative):65-73; discussion 73-74.
7. Schuette AJ, Cawley CM, Barrow DL. Indocyanine green videoangiography in the management of dural arteriovenous fistulae. *Neurosurgery*. 2010;67(3):658-662; discussion 662.
8. Takagi Y, Sawamura K, Hashimoto N, Miyamoto S. Evaluation of serial intraoperative surgical microscope-integrated intraoperative near-infrared indocyanine green videoangiography in patients with cerebral arteriovenous malformations. *Neurosurgery*. 2012;70(1 suppl operative):34-42; discussion 42-43.
9. Schubert GA, Seiz-Rosenhagen M, Ortler M, Czabanka M, Scheufler KM, Thome C. Cortical ICG videography for quantification of acute hypoperfusion after subarachnoid hemorrhage: a feasibility study. *Neurosurgery*. 2012;71(2 suppl operative):260-267; discussion 267-268.
10. Uchino H, Nakamura T, Houkin K, Murata J-I, Saito H, Kuroda S. Semi-quantitative analysis of indocyanine green videoangiography for cortical perfusion assessment in superficial temporal artery to middle cerebral artery anastomosis. *Acta Neurochir (Wien).* 2013;155(4):599-605.

For many years, cerebrovascular neurosurgeons have had to rely on the external morphological appearance of blood vessels to infer their lumen diameter and thus their flow. This has inherent limitations because it is possible to have physiologically meaningful changes in lumen size that are not apparent from outside inspection. This is particularly true in bypass surgery because a bypass can appear full and pulsatile and be completely occluded. Naturally, the purpose of seeing the flow is to ensure that it is adequate to meet the metabolic demands of the brain. The rapid adoption of indocyanine green (ICG) videoangiography (ICG-VA) in neurosurgery reflects the strong desire of neurosurgeons to know the flow status of vessels. ICG-VA is a rapid, flexible, and repeatable method for evaluating flow in vessels within the operative field. With experience, it has become clear that the information the ICG-VA provides about flow is largely qualitative. It shows vessel filling, but even excellent filling does not ensure a rate of flow that will sustain the brain. A variety of techniques are in development either to provide quantitative flow in both individual vessels and in regions of brain parenchyma or to evaluate the metabolism of the brain. At present, none of these provide the simplicity and availability of ICG.

The present study aims to determine whether a commercially available software package paired with ICG angiography (FLOW®800) can enhance the information that ICG-VA alone gives us. The software analyzes the visualized field in terms of the intensity of pixels, which is a reflection of the amount of ICG in the vessels. The result produces timing curves, showing order (and therefore direction) of flow, or colored timing maps, showing the relative timing of entry of ICG into exposed regions of brain. The authors used laser speckle imaging and quantitative Doppler as comparisons, if not exactly as controls. They show that there is some ability to see changes in hemodynamics in a qualitative sense but not to make quantitative determinations. This makes its primary utility the making of intrapatient comparisons in the same case (ie, before and after bypass or to reassess flow in a bypass during the same operation). Methodologically, the authors used $t_{1/2max}$ to determine timing because it is not dependent on absolute intensity. The distinctions made by $t_{1/2max}$ are often finer than can be made by the eye.

Ultimately, this software has many limits for the evaluation of bypasses. However, it is still compelling because it is convenient and makes distinctions we cannot make just by watching the video alone. Such a flow method that provides snapshots of qualitative data in a limited field is a distant second best to a dynamic, constantly updated method that delivers quantitative data. But until the latter becomes practical and easily available, this is a valuable incremental step.

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